

and claim 25 has been amended to substantially include the recitations of its parent claims therein.

Reconsideration and allowance of the application are respectfully requested.

#### **Discussion Of May 22, 2003 Interview**

Applicants express appreciation for the courtesies extended by the Examiner during a May 22, 2003 interview at the Patent and Trademark Office with Arnold Turk. During the interview, Applicants' invention as disclosed in the originally filed application and as recited in Applicants' claims was discussed. Moreover, the rejections set forth in the November 25, 2002 Office Action were discussed.

Thus, the rejections under 35 U.S.C. 112, first paragraph, were discussed with the Examiner's attention being directed to the originally filed disclosure including the Background Art section and page 19. The Examiner agreed that such arguments would be favorably considered.

Moreover, with respect to the prior art rejection based upon Nishigaki et al., it was submitted that Nishigaki et al. does not disclose the use of a second antimicrobial agent, and that the compounds of the present invention have improved properties based on their ability as drug efflux pump inhibitors.

Still further, it was indicated that claims may be added directed to inhibiting drug resistance acquisition due to a drug efflux pump, and the Examiner indicated that such claims would be favorably considered.

Arguments presented during the interview are included in the remarks below.

**Response To Indication Of Allowable Subject Matter**

Applicants express appreciation for the indication that claims 1-3 and 5 are allowed, and that claims 8-11, 24 and 25 would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claim. However, for the reasons set forth below each of the pending claims is in condition for allowance. Accordingly, allowance of each of the pending claims with the early mailing of the Notices of Allowance and Allowability is respectfully requested.

**Response to Rejections Under 35 U.S.C. 112, First Paragraph**

Claim 4 is rejected under 35 U.S.C. § 112, first paragraph, because the Examiner asserts that while the specification is enabling for therapeutic treatment of microbial infection when the compound is used together with an antimicrobial agent, it does not reasonably provide enablement for the "preventive treatment" of the microbial infection, etc.

Claims 6, 7, 12-18, 20-23, 26 and 27 are rejected under 35 U.S.C. § 112, first paragraph, because the Examiner asserts that while the specification is enabling for therapeutic treatment of microbial infection when the compound is used together with an antimicrobial agent, it does not reasonably provide enablement for the "preventive treatment" of the microbial infection or the "therapeutic treatment" of the microbial infection when the compound is administered without an antibacterial agent.

In response, Applicants respectfully submit that the preventive treatment of microbial infection is enabled whereby one having ordinary skill in the art would be capable of practicing Applicants' invention without undue experimentation. In this regard, as discussed with the Examiner during the above-noted interview and as pointed out in Applicants' specification, for example, in the Background Art section, it is known in the art that various antibacterial agents can be used both in the preventive or therapeutic treatment of infectious diseases caused by microorganisms. However, with the increase of clinically used amount of antibacterial agents, remarkable numbers of resistant bacterial strains to these preventive and therapeutic antibacterial agents have emerged, which becomes a serious problem in the treatment of infectious diseases.

Moreover, it is disclosed in the Background Art section of Applicants' specification that recently the presence of drug efflux pumps has been recognized as a bacterial excretion mechanism of drugs through researches on resistance acquiring mechanisms of resistant bacteria. Thus, in aspects of Applicants' invention, the resistance of bacteria is eliminated by inhibiting the drug efflux pump so as to improve preventive and/or therapeutic effect of the antimicrobial agent. For example, as previously pointed out by Applicants, Applicants' invention can enhance antibacterial action of an antibacterial agent, and on the basis of this action, one of ordinary skill in the art would readily understand that Applicants' invention can prevent formation of a bacterial infection in combination with an antibacterial agent, because every kind of antibacterial agent inherently has preventive action of formation of infection based on its antibacterial activity. Moreover, as explained in the specification, the claimed medicament also prevents formation of

resistance of bacteria to antibacterial agents, and can eliminate already acquired resistance from resistant bacteria which can also have a preventive action.

Accordingly, one having ordinary skill in the art would be capable of practicing Applicants' invention without undue experimentation as a preventive treatment, whereby the rejection of record should be withdrawn.

Moreover, Applicants note that as disclosed, for example, at page 19, first full paragraph of Applicants' specification, methods for using the medicament of the present invention are not particularly limited. For example, it is disclosed that the method can include administering one or more antimicrobial agents, and also administering the medicament of the present invention simultaneously, separately, or successively to enhance the activity of the antimicrobial agents. Thus, the method of the present invention also includes the separate administration of the antimicrobial agent, and Applicants' claims can be directed to methods of treatment of microbial infection which recites the administration of Applicants' recited compositions as part of a treatment method with or without antimicrobial agents being present.

Accordingly, one having ordinary skill in the art would be capable of practicing Applicants' invention without undue experimentation wherein Applicants' compounds are administered without an antibacterial agent.

In view of the above, these grounds of rejection should be withdrawn.

**Response to Rejection Under 35 U.S.C. 103(a)**

Claims 19, 21, 23 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nishigaki et al. (hereinafter "Nishigaki") (Chem. Pharm. Bull. 1975). In this ground of rejection, it is asserted that Nishigaki teaches certain 1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid compounds, referring to the formula Table I, page 3172 that are useful as antibacterial agents and the species of Compound No. 45. The rejection asserts that the instant claims differ by reciting R<sup>14</sup> to be an alkyl group having 1, 3 or 4 carbon atoms whereby the instant compounds differ from the reference compound by a -CH<sub>2</sub> groups (when R<sup>14</sup> is alkyl having 1 or 3 carbon atoms), and thus, the instant compounds are homologs of the reference compound. The rejection concludes that one having ordinary skill in the art would have been motivated to prepare instantly claimed compounds because such structurally similar compounds are expected to possess similar properties.

In response, Applicants respectfully submit that one having ordinary skill in the art would not have been motivated following the disclosure of Nishigaki to modify Compound No. 45 in the manner asserted in the rejection. In this regard, Applicants note that Nishigaki discloses a lengthy list of antibacterials, and does not provide any teaching or suggestion for picking and choosing one antibacterial from amongst the plethora of antibacterials disclosed therein, modifying this particularly selected antibacterial, and modifying the particularly selected antibacterial in the manner asserted in the rejection.

Despite the above deficiencies in the rejection of record, without expressing any agreement and/or acquiescence with the rejection, and in an attempt to advance prosecution of

the application, claims 19, 21 and 23 have been canceled without prejudice or disclaimer of the subject matter recited therein.

With respect to claim 25, Applicants note that this claim is directed to a method for therapeutic treatment of a microbial infection comprising administering to a mammal in need thereof a therapeutically effective amount of a composition comprising a compound represented by the formula recited in claim 25 or a physiologically acceptable salt thereof as an active ingredient and at least one antimicrobial agent. Nishigaki does not teach or suggest this method.

In this regard, as noted above, it would not have been obvious to one having ordinary skill in the art to arrive at compounds as recited in Applicants' canceled claim 19. Moreover, there is no teaching or suggestion in Nishigaki to utilize any of the antibacterials disclosed therein in combination, let alone Compound No. 45 in combination with other compounds disclosed therein. Accordingly, a *prima facie* case of obviousness has not been established whereby this ground of rejection should be withdrawn.

Still further, Applicants note that even if a *prima facie* case of obvious were established, , the presently claimed invention yields unexpected results sufficient to overcome a *prima facie* case of obviousness. In this regard, In re Soni, 34 U.S.P.Q.2d 1684, 1687-1688 (Fed. Cir. 1995), held that a showing of substantially improved results for invention, and a statement that results were unexpected suffices to establish unexpected results absent evidence to the contrary. Id. at 1687-88. In this regard, Applicants establish throughout their originally filed application, including the Examples presented therein, the unexpected results associated with the combination of ingredients recited in Applicants' method. Thus, in one aspect of Applicants'

invention, Applicants' recited compounds eliminate the resistance of the bacteria by inhibiting a drug efflux pump so as to improve preventive and/or therapeutic effect of the antimicrobial agent. Accordingly, Applicants' recited method for therapeutic treatment of a microbial infection comprising administering to a mammal in need thereof a therapeutically effective amount of a composition comprising a compound represented by the formula recited in claim 25 or a physiologically acceptable salt thereof as an active ingredient and at least one antimicrobial agent is patentable over the prior art of record.

In view of the above, this ground of rejection should be withdrawn.

#### CONCLUSION

For the reasons advanced above, Applicants respectfully submit that all pending claims patentably define Applicants' invention.

Allowance of the application with an early mailing date of the Notice of Allowance and allowability is therefore respectfully requested.

Should the Examiner have any further comments or questions, the Examiner is invited to contact the undersigned at the below-listed telephone number.

Respectfully submitted,  
Kiyoshi NAKAYAMA et al.

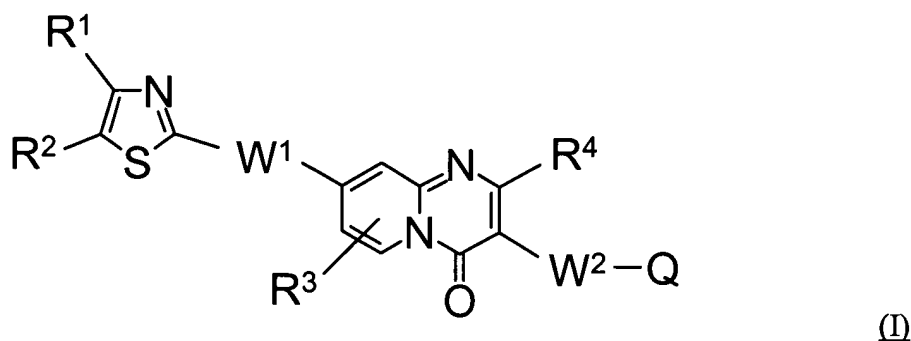
  
Bruce H. Bernstein

Reg. No. 29,027

May 27, 2003  
GREENBLUM & BERNSTEIN, P.L.C.  
1950 Roland Clarke Place  
Reston, VA 20191  
(703) 716-1191

**APPENDIX**  
**MARKED-UP COPY OF AMENDED CLAIMS 1, 5, 12, 18 AND 25**

1. (Twice Amended) A compound represented by the following formula (I) or a physiologically acceptable salt thereof, or a hydrate thereof:



wherein,  $R^1$  and  $R^2$  each independently represent hydrogen atom, a halogen atom, hydroxyl group, a group of  $OZ_{1-6}$  (the group of  $OZ_{1-6}$  represents an alkyl group having 1-6 carbon atoms or a fluoroalkyl group having 1-6 carbon atoms, which bonds via the oxygen atom), a group of  $S(O)_nZ_{1-4}$  ( $Z_{1-4}$  represents an alkyl group having 1-4 carbon atoms or a fluoroalkyl group having 1-4 carbon atoms or an alkylene group derived therefrom), a group of  $N(R^{12})(R^{13})$  ( $R^{12}$  and  $R^{13}$  each independently represent hydrogen atom, an alkyl group having 1-4 carbon atoms or a fluoroalkyl group having 1-4 carbon atoms), a group of  $Z_{1-8}$  which may be substituted ( $Z_{1-8}$  represents an alkyl group having 1-8 carbon atoms or a fluoroalkyl group having 1-8 carbon atoms), a 5- to 7-membered cyclic alkyl group, an aryl group, a heteroaryl group, or a 4- to 7-membered saturated or partially saturated heterocyclic group (the cyclic alkyl group, aryl group, heteroaryl group and heterocyclic group may have one to three substituents selected from the



group consisting of a halogen atom, hydroxyl group, a group of  $OZ_{1-4}$ , a group of  $S(O)_nZ_{1-4}$ , a group of  $N(R^{12})(R^{13})$ , a group of  $Z_{1-4}$ , carboxyl group, a group of  $CO_2Z_{1-4}$ , group of  $CONH_2$ , a group of  $CONH(Z_{1-4})$  and a group of  $CON(Z_{1-4})(Z_{1-4})$ ;

$W^1$  represents a group selected from the group consisting of  $-CH=CH-$ ,  $-N(R^{12})CO-$ ,  $-CON(R^{12})-$ ,  $-CH_2O-$  and  $-CH_2CH_2-$  (each of the aforementioned groups binds to the thiazole ring at the left end);

$R^3$  represents hydrogen atom, a halogen atom, hydroxyl group or an amino group;

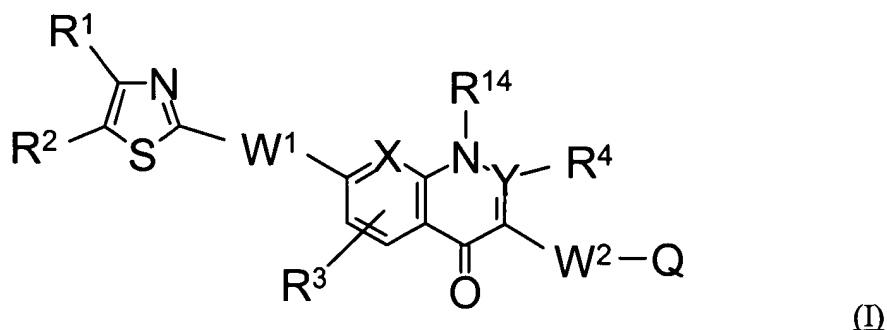
$R^4$  represents a group selected from the group consisting of hydrogen atom, a group of  $-OZ_{0-4}R^5$  ( $Z_{0-4}$  represents an alkylene group having 1-4 carbon atoms, a fluorine-substituted alkylene group having 1-4 carbon atoms or a single bond, and  $R^5$  represents a 5- to 7-membered cyclic alkyl group, an aryl group, a heteroaryl group or a 4- to 7-membered saturated or partially saturated heterocyclic group (the cyclic alkyl group, aryl group, heteroaryl group and heterocyclic group may have one to three substituents selected from the group consisting of a halogen atom, hydroxyl group, a group of  $OZ_{1-4}$ , a group of  $S(O)_nZ_{1-4}$ , a group of  $N(R^{12})(R^{13})$ , a group of  $Z_{1-4}$ , carboxyl group, a group of  $CO_2Z_{1-4}$ , group of  $CONH_2$ , a group of  $CONH(Z_{1-4})$  and a group of  $CON(Z_{1-4})(Z_{1-4})$ ), a group of  $-S(O)_nZ_{0-4}R^5$ , a group of  $-N(R^6)(R^7)$  ( $R^6$  and  $R^7$  each independently represent hydrogen atom or  $Z_{1-4}$ , or they may bind to each other to form a saturated or unsaturated 5- to 7-membered ring (the ring may contain one or two hetero atoms as ring constituting atoms), and  $R^6$  and  $R^7$  may have one to three substituents selected from the group consisting of a halogen atom, hydroxyl group, a group of  $OCON(R^{12})(R^{13})$ , a group of  $CON(R^{12})(R^{13})$ , a group of  $N(R^{12})CON(R^{12})(R^{13})$ , a group of  $Z_{1-4}$ , a group of  $OZ_{1-4}$ , a group

S(O)<sub>n</sub>Z<sub>1-4</sub>, group of CH<sub>2</sub>OH, a group of (CH<sub>2</sub>)<sub>m</sub>N(R<sup>12</sup>)(R<sup>13</sup>), carboxyl group, cyano group, a group of CO-Z<sub>1-4</sub>(R<sup>10</sup>)-N(R<sup>12</sup>)(R<sup>13</sup>) (R<sup>10</sup> is a substituent corresponding to a side chain on an amino acid carbon or a group of -Z<sub>1-4</sub>-R<sup>11</sup> (R<sup>11</sup> represents a substituent which forms a quaternary salt) and a

group of  $\begin{array}{c} \text{CO} \cdot \text{Z}_{1-4} \cdot \text{N}(\text{R}^{12})(\text{R}^{13}) \\ | \\ (\text{CH}_2)_q \end{array}$  }, a 5- or 6-membered aryl group which may be substituted and a 5- or 6-membered unsaturated heterocyclic group which may be substituted;

W<sup>2</sup> represents a single bond or -C(R<sup>8</sup>)=C(R<sup>9</sup>)- (R<sup>8</sup> and R<sup>9</sup> each independently represent hydrogen atom, a halogen atom, a lower alkyl group, an alkoxy group, cyano group, carboxyl group, hydroxymethyl group, cyanomethyl group, vinyl group or a group of N(R<sup>12</sup>)(R<sup>13</sup>)), Q represents an acidic group, and W<sup>2</sup> and Q may bind together to form vinylidenethiazolidinedione in *E*- or *Z*-configuration or an equivalent heterocyclic ring; m and n each independently represent an integer of 0 to 2, and q represents an integer of 0 to 3.

5. (Twice Amended) A compound represented by the following formula (I) or a physiologically acceptable salt thereof, or hydrate thereof



wherein, R<sup>1</sup> and R<sup>2</sup> each independently represent hydrogen atom, a halogen atom, hydroxyl group, a group of OZ<sub>1-6</sub> (the group of OZ<sub>1-6</sub> represents an alkyl group having 1-6 carbon atoms or

a fluoroalkyl group having 1-6 carbon atoms, which bonds via the oxygen atom), a group of  $S(O)_nZ_{1-4}$  ( $Z_{1-4}$  represents an alkyl group having 1-4 carbon atoms or a fluoroalkyl group having 1-4 carbon atoms or an alkylene group derived therefrom), a group of  $N(R^{12})(R^{13})$  ( $R^{12}$  and  $R^{13}$  each independently represent hydrogen atom, an alkyl group having 1-4 carbon atoms or a fluoroalkyl group having 1-4 carbon atoms), a group of  $Z_{1-8}$  which may be substituted ( $Z_{1-8}$  represents an alkyl group having 1-8 carbon atoms or a fluoroalkyl group having 1-8 carbon atoms), a 5- to 7-membered cyclic alkyl group, an aryl group, a heteroaryl group, or a 4- to 7-membered saturated or partially saturated heterocyclic group (the cyclic alkyl group, aryl group, heteroaryl group and heterocyclic group may have one to three substituents selected from the group consisting of a halogen atom, hydroxyl group, a group of  $OZ_{1-4}$ , a group of  $S(O)_nZ_{1-4}$ , a group of  $N(R^{12})(R^{13})$ , a group of  $Z_{1-4}$ , carboxyl group, a group of  $CO_2Z_{1-4}$ , group of  $CONH_2$ , a group of  $CONH(Z_{1-4})$  and a group of  $CON(Z_{1-4})(Z_{1-4})$ );

$W^1$  represents a group selected from the group consisting of  $-CH=CH-$ ,  $-N(R^{12})CO-$ ,  $-CON(R^{12})-$ ,  $-CH_2O-$  and  $-CH_2CH_2-$  (each of the aforementioned groups binds to the thiazole ring at the left end);

$R^3$  represents hydrogen atom, a halogen atom, hydroxyl group or an amino group;

$R^4$  represents a group selected from the group consisting of hydrogen atom, a group of  $-OZ_{0-4}R^5$  ( $Z_{0-4}$  represents an alkylene group having 1-4 carbon atoms, a fluorine-substituted alkylene group having 1-4 carbon atoms or a single bond, and  $R^5$  represents a 5- to 7-membered cyclic alkyl group, an aryl group, a heteroaryl group or a 4- to 7-membered saturated or partially saturated heterocyclic group (the cyclic alkyl group, aryl group, heteroaryl group and heterocyclic group

may have one to three substituents selected from the group consisting of a halogen atom, hydroxyl group, a group of  $OZ_{1-4}$ , a group of  $S(O)_nZ_{1-4}$ , a group of  $N(R^{12})(R^{13})$ , a group of  $Z_{1-4}$ , carboxyl group, a group of  $CO_2Z_{1-4}$ , group of  $CONH_2$ , a group of  $CONH(Z_{1-4})$  and a group of  $CON(Z_{1-4})(Z_{1-4})$ , a group of  $-S(O)_nZ_{0-4}R^5$ , a group of  $-N(R^6)(R^7)$  ( $R^6$  and  $R^7$  each independently represent hydrogen atom or  $Z_{1-4}$ , or they may bind to each other to form a saturated or unsaturated 5- to 7-membered ring (the ring may contain one or two hetero atoms as ring constituting atoms), and  $R^6$  and  $R^7$  may have one to three substituents selected from the group consisting of a halogen atom, hydroxyl group, a group of  $OCON(R^{12})(R^{13})$ , a group of  $CON(R^{12})(R^{13})$ , a group of  $N(R^{12})CON(R^{12})(R^{13})$ , a group of  $Z_{1-4}$ , a group of  $OZ_{1-4}$ , a group  $S(O)_nZ_{1-4}$ , group of  $CH_2OH$ , a group of  $(CH_2)_mN(R^{12})(R^{13})$ , carboxyl group, cyano group, a group of  $CO-Z_{1-4}(R^{10})-N(R^{12})(R^{13})$  ( $R^{10}$  is a substituent corresponding to a side chain on an amino acid carbon or a group of  $-Z_{1-4}-R^{11}$  ( $R^{11}$  represents a substituent which forms a quaternary salt) and a

group of  $\begin{array}{c} CO-Z_{1-4}-N(R^{12})(R^{13}) \\ | \\ (CH_2)_q \end{array}$  }, a 5- or 6-membered aryl group which may be substituted and a 5- or 6-membered unsaturated heterocyclic group which may be substituted;

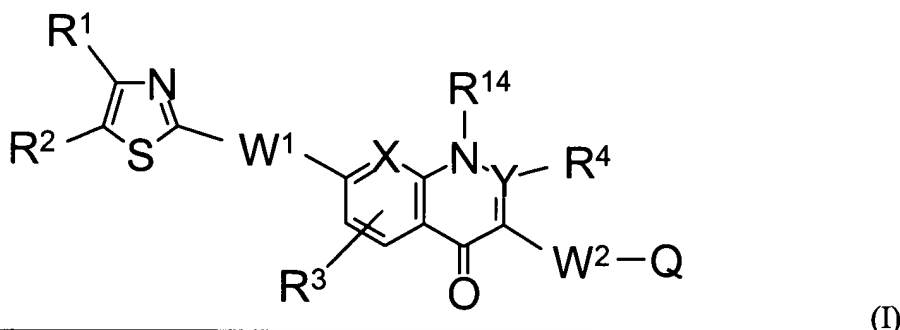
$W^2$  represents a single bond or  $-C(R^8)=C(R^9)-$  ( $R^8$  and  $R^9$  each independently represent hydrogen atom, a halogen atom, a lower alkyl group, an alkoxy group, cyano group, carboxyl group, hydroxymethyl group, cyanomethyl group, vinyl group or a group of  $N(R^{12})(R^{13})$ ),  $Q$  represents an acidic group, and  $W^2$  and  $Q$  may bind together to form vinylidenethiazolidinedione in *E*- or *Z*-configuration or an equivalent heterocyclic ring;  $m$  and  $n$  each independently represent an integer of 0 to 2, and  $q$  represents an integer of 0 to 3;  $R^{14}$  represents hydrogen atom,  $Z_{1-4}$ ,  $Z_{1-4}R^5$  or

$Z_{1-4}OR^5$ ; and X represents C-H and Y represents C-H or nitrogen atom.

12. (Amended) The method according to claim 7 wherein the mammal is a human.

18. (Amended) The method according to claim 13 wherein the mammal is a human.

25. (Amended) [The] A method for therapeutic treatment of a microbial infection comprising administering to a mammal in need thereof a therapeutically effective amount of a composition comprising a compound represented by formula (I) or a physiologically acceptable salt thereof as an active ingredient and [according to claim 23, further comprising administering] at least one antimicrobial agent



wherein,  $R^1$  and  $R^2$  each independently represent hydrogen atom, a halogen atom, hydroxyl group, a group of  $OZ_{1-6}$  (the group of  $OZ_{1-6}$  represents an alkyl group having 1-6 carbon atoms or a fluoroalkyl group having 1-6 carbon atoms, which bonds via the oxygen atom), a group of  $S(O)_nZ_{1-4}$  ( $Z_{1-4}$  represents an alkyl group having 1-4 carbon atoms or a fluoroalkyl group having 1-4 carbon atoms or an alkylene group derived therefrom), a group of  $N(R^{12})(R^{13})$  ( $R^{12}$  and  $R^{13}$  each independently represent hydrogen atom, an alkyl group having 1-4 carbon atoms or a fluoroalkyl group having 1-4 carbon atoms), a group of  $Z_{1-8}$  which may be substituted ( $Z_{1-8}$  represents an alkyl group having 1-8 carbon atoms or a fluoroalkyl group having 1-8 carbon

atoms), a 5- to 7-membered cyclic alkyl group, an aryl group, a heteroaryl group, or a 4- to 7-membered saturated or partially saturated heterocyclic group (the cyclic alkyl group, aryl group, heteroaryl group and heterocyclic group may have one to three substituents selected from the group consisting of a halogen atom, hydroxyl group, a group of  $OZ_{1-4}$ , a group of  $S(O)_nZ_{1-4}$ , a group of  $N(R^{12})(R^{13})$ , a group of  $Z_{1-4}$ , carboxyl group, a group of  $CO_2Z_{1-4}$ , group of  $CONH_2$ , a group of  $CONH(Z_{1-4})$  and a group of  $CON(Z_{1-4})(Z_{1-4})$ );

$W^1$  represents a group selected from the group consisting of  $-CH=CH-$ ,  $-N(R^{12})CO-$ ,  $-CON(R^{12})-$ ,  $-CH_2O-$  and  $-CH_2CH_2-$  (each of the aforementioned groups binds to the thiazole ring at the left end);

$R^3$  represents hydrogen atom, a halogen atom, hydroxyl group or an amino group;

$R^4$  represents a group selected from the group consisting of hydrogen atom, a group of  $-OZ_{0-4}R^5$  ( $Z_{0-4}$  represents an alkylene group having 1-4 carbon atoms, a fluorine-substituted alkylene group having 1-4 carbon atoms or a single bond, and  $R^5$  represents a 5- to 7-membered cyclic alkyl group, an aryl group, a heteroaryl group or a 4- to 7-membered saturated or partially saturated heterocyclic group (the cyclic alkyl group, aryl group, heteroaryl group and heterocyclic group may have one to three substituents selected from the group consisting of a halogen atom, hydroxyl group, a group of  $OZ_{1-4}$ , a group of  $S(O)_nZ_{1-4}$ , a group of  $N(R^{12})(R^{13})$ , a group of  $Z_{1-4}$ , carboxyl group, a group of  $CO_2Z_{1-4}$ , group of  $CONH_2$ , a group of  $CONH(Z_{1-4})$  and a group of  $CON(Z_{1-4})(Z_{1-4})$ ), a group of  $-S(O)_nZ_{0-4}R^5$ , a group of  $-N(R^6)(R^7)$  ( $R^6$  and  $R^7$  each independently represent hydrogen atom or  $Z_{1-4}$ , or they may bind to each other to form a saturated or unsaturated 5- to 7-membered ring (the ring may contain one or two hetero atoms as ring

constituting atoms), and  $R^6$  and  $R^7$  may have one to three substituents selected from the group consisting of a halogen atom, hydroxyl group, a group of  $OCON(R^{12})(R^{13})$ , a group of  $CON(R^{12})(R^{13})$ , a group of  $N(R^{12})CON(R^{12})(R^{13})$ , a group of  $Z_{1-4}$ , a group of  $OZ_{1-4}$ , a group of  $S(O)_nZ_{1-4}$ , group of  $CH_2OH$ , a group of  $(CH_2)_mN(R^{12})(R^{13})$ , carboxyl group, cyano group, a group of  $CO-Z_{1-4}(R^{10})-N(R^{12})(R^{13})$  ( $R^{10}$  is a substituent corresponding to a side chain on an amino acid carbon or a group of  $-Z_{1-4}-R^{11}$  ( $R^{11}$  represents a substituent which forms a quaternary salt) and a

group of  $\begin{array}{c} CO-Z_{1-4}-N(R^{12})(R^{13}) \\ | \\ (CH_2)_q \end{array}$  }, a 5- or 6-membered aryl group which may be substituted and a 5- or 6-membered unsaturated heterocyclic group which may be substituted;

$W^2$  represents a single bond or  $-C(R^8)=C(R^9)-$  ( $R^8$  and  $R^9$  each independently represent hydrogen atom, a halogen atom, a lower alkyl group, an alkoxy group, cyano group, carboxyl group, hydroxymethyl group, cyanomethyl group, vinyl group or a group of  $N(R^{12})(R^{13})$ ),  $Q$  represents an acidic group, and  $W^2$  and  $Q$  may bind together to form vinylidenethiazolidinedione in *E*- or *Z*-configuration or an equivalent heterocyclic ring;  $m$  and  $n$  each independently represent an integer of 0 to 2, and  $q$  represents an integer of 0 to 3;  $R^{14}$  represents hydrogen atom, an alkyl group having 1, 3 or 4 carbon atoms or a fluoroalkyl group having 1-4 carbon atoms,  $Z_{1-4}R^5$  or  $Z_{1-4}OR^5$ ; and  $X$  and  $Y$  each independently represent C-H or nitrogen atom.